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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/592,010	03/06/2007	Andreas Herrmann	50125/115001	7008

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
11/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/592,010	HERRMANN ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,12,15,19 and 21* is/are pending in the application.

4a) Of the above claim(s) *15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,12, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/592,010 is a 371 of PCT/EP05/03888 filed on 04/13/2005. Foreign application European Patent Office (EPO) 04008881.7 was filed on 04/14/2004.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-6, 10, 12, and 21, drawn to an expression system, containing one or more nucleic acid(s) comprising a) at least one nucleic acid for an IL- 15/Fc fusion protein, b) at least one promoter and c) at least one nucleic acid for a CD5 leader, the promoter and the nucleic acid for the CD5 leader being functionally linked to the nucleic acid for the IL- 15/Fc fusion protein (claim 1), a nucleic acid, containing the components a) to c) of claim 1 (claim 10); and a host cell, containing an expression system according to claim 1 or a nucleic acid according to claim 10 (claim 12) in the reply filed on 09/21/2009 is acknowledged. The traversal is on the ground(s) that as claim 15 is directed to a use of the product claimed in claim 1, unity of invention exists between Groups I and II. Accordingly, the requirement for restriction between these groups should be withdrawn. This is not found persuasive because as stated in the Restriction requirement mailed on 08/26/2009, Applicant's claims encompass multiple inventions, multiple products (Group I) and multiple methods (Groups II and III), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. The common technical feature in all groups is functionally linking the nucleic acid encoding the protein to the nucleic acid encoding the CD5 leader. However, this common technical feature cannot be a special technical feature under PCT Rule 13.2 because the feature is shown in the prior art. **Sutherland et al.** teaches CD5 leader

sequence was fused to the Fc of mouse IgG2c, and expressed transgenically under the control of the rat insulin promoter in C57BL/6 mice (See abstract, Sutherland et al., Protective effect of CTLA4Ig secreted by transgenic fetal pancreas allografts, *Transplantation*, 69(9):1806-12, 2000). Furthermore, as documented in the Restriction requirement mailed on 08/26/2009 regarding Unity of Invention Rejoinder, MPEP 1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04(a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

Claims 1-6, 10, 12, 15, 19, and 21 are pending. Claims 15 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-6, 10, 12, and 21 are currently under examination

The requirement is still deemed proper and is therefore made FINAL.

Priority

This application 11/592,010 filed on 03/06/2007, the filed Application data sheet filed on 03/06/2007 claims benefit of foreign application European Patent Office (EPO) 04008881.7 filed

on 04/14/2004. The Examiner acknowledges that Applicant has submitted on 09/07/2006 a certified copy of European Patent Office (EPO) 04008881.7 filed on 04/14/2004 under requirement of 35 U.S.C. 119 (a-d) conditions. However, it is noted that, the European Patent Office (EPO) 04008881.7 filed on 04/14/2004 is not in English. Therefore, without a certified translation of European Patent Office (EPO) 04008881.7, the effective filing date for the instant claims is 04/13/2005, the filing date of PCT/EP05/03888. Applicant cannot rely upon the foreign priority papers to overcome the rejection under 35 USC 102 (e) or 102 (a) as set forth below because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Objection

1. Claims 1-6, 10, and 12 are objected to because of the following informalities: Claims 1-6, 10, and 12 are missing an article (i.e. "a" or "an" or "the") in the beginning of these claims. For instance, "Expression system" recited in claim 1 should read "An expression system". Appropriate correction is required.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claim 1, 2, 4-6, 10, and 12 are rejected under 35 U.S.C. 102(a) and under 35 U.S.C. 102(e) as being anticipated by **Zheng et al.** (US Publication No. 2006/0057102, publication date 03/16/2006, filed on 08/11/2005, provisional applications filed on 08/11/2004).

Claim 1 is directed to an expression system, containing one or more nucleic acid(s) comprising a) at least one nucleic acid for an IL- 15/Fc fusion protein, b) at least one promoter and c) at least one nucleic acid for a CD5 leader, the promoter and the nucleic acid for the CD5 leader being functionally linked to the nucleic acid for the IL- 15/Fc fusion protein.

With regard to claims 1, 4, 10, 12, Zheng et al. teaches a mutant of human IL-15 is fused to a wild-type or mutant human IgG1 Fc region. This human IL-15/Fc chimera or any of the IL-15-containing antagonists described herein may be optionally linked to a CD5 leader sequence, as shown in FIG. 3 (i.e., a CD5 leader sequence having the following residues: MPMGSLQPLATLYLLGMLVASCLG (see paragraph [0048], Zheng et al.).

With regard to claims 2, 5, and 6, Zheng et al. teaches a plasmid carries a CMV promoter/enhancer, a bovine growth hormone polyadenylation signal and a neomycin resistance gene for selection with G418 (see paragraph [0074], Zheng et al.).

Thus, Zheng et al. clearly anticipates claims 1, 2, 4-6, 10, and 12 of instant application.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 4, 6, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ferrari-Lacraz et al.** (Ferrari-Lacraz et al. An antagonist IL-15/Fc protein prevents costimulation blockade-resistant rejection, *J. Immunol.* 167(6):3478-85, 2001) in view of **Sutherland et al.** (Sutherland et al., Protective effect of CTLA4Ig secreted by transgenic fetal pancreas allografts, *Transplantation*, 69(9):1806-12, 2000; This reference is cited in the IDS filed on 11/13/2006).

Claim 1 is directed to an expression system, containing one or more nucleic acid(s) comprising a) at least one nucleic acid for an IL- 15/Fc fusion protein, b) at least one promoter and c) at least one nucleic acid for a CD5 leader, the promoter and the nucleic acid for the CD5 leader being functionally linked to the nucleic acid for the IL- 15/Fc fusion protein.

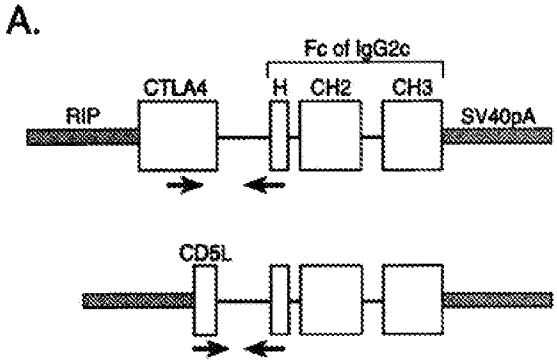
Ferrari-Lacraz et al. teaches an IL-15 mutant/Fcγ2a protein, a potentially cytolytic protein that is also a high-affinity receptor site specific antagonist for the IL-15Rα receptor protein, as a therapeutic agent. The IL-15-related fusion protein was used as monotherapy or in combination with CTLA4/Fc in murine islet allograft models. As monotherapies, CTLA4/Fc and an IL-15 mutant/Fcγ2a were comparably effective in a semiallogeneic model system, and

combined treatment with IL-15 mutant/Fcγ2a plus CTLA4/Fc produced universal permanent engraftment (See abstract, Ferrari-Lacraz et al., 2001).

With regard to the limitation "Fc part of the fusion protein is an Fc fragment of an immunoglobin G" recited in claim 4 of instant application, Ferrari-Lacraz et al. teaches that an IgG2a protein bearing the same Fc sequences as CTLA4/Fc and IL-15 mutant/Fcγ2a protein was used as a control (See left column, page 3479, Ferrari-Lacraz et al.)

Ferrari-Lacraz et al. does not explicitly teach a promoter expressing the IL-15/Fc fusion protein and the limitation CD5 leader being functionally linked to the nucleic acid for the IL-15/Fc fusion protein recited in claim 1, and the polyadenylation signal recited in claim 6.

Sutherland et al. teaches cDNA encoding the murine CTLA4 was fused to IgG2c Fc (CTLA4Ig) and CD5 leader sequence was fused to the Fc of mouse IgG2c (control CD5LIg) with SV40 polyadenylation signal (SV40pA), and expressed transgenically under the control of the rat insulin promoter (RIP) in C57BL/6 mice (See Materials and methods, Fig. 3A, shown below, Sutherland et al., 2000).



Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Ferrari-Lacraz et al. regarding as

monotherapies, CTLA4/Fc and an IL-15 mutant/Fcgamma2a fusion proteins are comparably effective in a semiallogeneic model system, with the teachings of Sutherland et al. regarding cDNA encoding the murine CTLA4 was fused to IgG2c Fc (CTLA4Ig) and CD5 leader sequence was fused to the Fc of mouse IgG2c (control CD5LIg), and expressed transgenically under the control of the rat insulin promoter (RIP) for allografts, to arrive at the claimed methods recited in claims 1, 4, 6, 10, and 12 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Ferrari-Lacraz et al. and the teachings of Sutherland et al. because Sutherland et al. teaches CD5 leader sequences can be fused to CTLA4/IgG2c Fc fusion for allograft purpose and a promoter to direct the expression of CTLA4/IgG2c Fc fusion protein.

There would have been a reasonable expectation of success given (i) successful demonstration of CTLA4/Fc and an IL-15 mutant/Fcγ2a fusion proteins, as monotherapies, are comparably effective in a semiallogeneic model system, by the teachings of Ferrari-Lacraz et al., (ii) successfully demonstration of cDNA encoding the murine CTLA4 was fused to IgG2c Fc (CTLA4Ig) and CD5 leader sequence was fused to the Fc of mouse IgG2c (control CD5LIg), and expressed transgenically under the control of the rat insulin promoter (RIP) for allografts, by the teachings of Sutherland et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

4. Claims 2, 3, 5, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ferrari-Lacraz et al.** (Ferrari-Lacraz et al. An antagonist IL-15/Fc protein prevents costimulation blockade-resistant rejection, *J. Immunol.* 167(6):3478-85, 2001) in view of

Sutherland et al. (Sutherland et al., Protective effect of CTLA4Ig secreted by transgenic fetal pancreas allografts, *Transplantation*, 69(9):1806-12, 2000; this reference is cited in the IDS filed on 11/13/2006) as applied to claims 1, 4, 6, 10, and 12 above, and further in view of **Kim et al.** (US patent 7,279,568, issued on 10/09/2007, filed on 05/06/2003).

The teachings of Ferrari-Lacraz et al. and Sutherland et al. have been discussed in the preceding section of the rejection of claims 1, 4, 6, 10, and 12 under 35 U.S.C. 103(a) as being unpatentable over Ferrari-Lacraz et al. (2001) in view of Sutherland et al. (2000).

Neither Ferrari-Lacraz et al. (2001) nor Sutherland et al. (2000) explicitly teaches "a selectable marker gene" recited in claim 5, and a CMV promoter with intron A being part of a transcription-regulating unit as recited in claims 2, 3, and 21.

However, at the time of filing of instant application, a selectable marker gene and a CMV promoter with intron A being part of a transcription-regulating unit were known in the art. For instant, **Kim et al.** teaches a chimeric expression vector having the advantages of both pCN and pEF vectors. Particularly, the chimeric expression vector pCEF of the present invention is constructed by inserting the enhancer region of HCMV IE gene into upstream of the EF1α gene promoter of pEF vector while maintaining the EF1α gene-derived transcription regulatory element comprising the promoter, the entire exon 1 sequence, the entire intron A sequence and the nucleotide sequence just before the initiation codon ATG of exon 2, which results in a high level of gene expression both in transient and stable expression systems (See lines 9-20, column 4, and Example 1, Kim et al.). Kim et al. teaches Neomycin resistant gene as a selectable marker (See for instance, Fig. 13 and Example 1, Kim et al.)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Kim et al. regarding CMV promoter with intron A as a transcription-regulating unit and neomycin resistant gene, into the combined teachings of Ferrari-Lacraz et al. (2001) and Sutherland et al. (2000) directing to an expression system, containing one or more nucleic acid(s) comprising a) at least one nucleic acid for an IL-15/Fc fusion protein, b) at least one promoter and c) at least one nucleic acid for a CD5 leader, the promoter and the nucleic acid for the CD5 leader being functionally linked to the nucleic acid for the IL- 15/Fc fusion protein, to arrive at the claimed expression system recited in claims 2, 3, 5, and 21.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Kim et al. into the combined teachings of Ferrari-Lacraz et al. (2001) and Sutherland et al. (2000) because Kim teaches that gene expression controlled by CMV promoter with intron A as a transcription-regulating unit leads to a high level of gene expression both in transient and stable expression systems.

There would have been a reasonable expectation of success given **(i)** successful establishment of an expression system, containing one or more nucleic acid(s) comprising a) at least one nucleic acid for an IL- 15/Fc fusion protein, b) at least one promoter and c) at least one nucleic acid for a CD5 leader, the promoter and the nucleic acid for the CD5 leader being functionally linked to the nucleic acid for the IL-15/Fc fusion protein, by the combined teachings of Ferrari-Lacraz et al. (2001) and Sutherland et al. (2000), and **(ii)** the construction of expression vector having gene of interest expressed by a CMV promoter with intron A as a

transcription-regulating unit would lead to a high level of gene expression both in transient and stable expression systems, by the teachings of Kim et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private

PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632